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(54) Title: NANOPARTICULATE STEROL FORMULATIONS AND STEROL COMBINATIONS

(57) Abstract: The present invention is directed to nanoparticulate compositions comprising one or more sterols or stanols, such as sitosterol or phytosterol. The sterol particles of the composition have an effective average particle size of less than about 2000 nm. In another aspect of this invention, novel combinations of sterols and other cholesterol lowering agents are described and methods of using same are taught.

NANOPARTICULATE STEROL FORMULATIONS AND STEROL COMBINATIONS

FIELD OF THE INVENTION

The present invention relates to nanoparticulate compositions comprising sterols and/or stanols, collectively referred to as "sterols," and novel sterol/stanol combinations. The nanoparticulate sterol particles preferably have an effective average particle size of less than about 2000 nm. In another aspect, this invention includes novel combinations of sterols and other cholesterol lowering agents and methods of using the same.

BACKGROUND OF THE INVENTION

I. Background Regarding Nanoparticulate Active Agent Compositions

Nanoparticulate active agent compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto, or associated with, the surface thereof a non-crosslinked surface stabilizer. Many factors can affect bioavailability including the dosage form and various properties, *e.g.*, dissolution rate of the drug. Poor bioavailability is a significant problem encountered in the development of pharmaceutical compositions, particularly those containing an active ingredient that is poorly soluble in water. By decreasing the particle size of an active agent, the surface area of the composition is increased, thereby generally resulting in an increased bioavailability. The '684 patent does not teach nanoparticulate compositions of sterols.

Methods of making nanoparticulate active agent compositions are described in, for example, U.S. Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388, for "Continuous Method of

Grinding Pharmaceutical Substances;" and U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." None of these patents teach nanoparticulate compositions of sterols.

Nanoparticulate active agent compositions are also described, for example, in U.S. Patent Nos. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,518,738 for "Nanoparticulate NSAID Formulations;" 5,521,218 for "Nanoparticulate

Iododipamide Derivatives for Use as X-Ray Contrast Agents;" 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus

(HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" 6,431,478 for "Small Scale Mill;" and 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," all of which are specifically incorporated by reference. In addition, U.S. Patent Application No. 20020012675 A1, published on January 31, 2002, for "Controlled Release Nanoparticulate Compositions," describes nanoparticulate compositions, and is specifically incorporated by reference. None of these patents teach nanoparticulate compositions of sterols.

Amorphous small particle compositions are described, for example, in U.S. Patent Nos. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

II. Background Regarding Sterols

Plant sterols have been used as dietary supplements for the reduction of serum cholesterol levels. High LDL cholesterol levels have been shown to be an important risk factor in the development of arteriosclerosis and ischaemic heart disease. Thus, lowering blood serum cholesterol levels for subjects at risk of such conditions is desirable.

Typically it has been necessary to incorporate sterols in a suitable material, such as a margarine, in which the waxy nature of the sterol can be tolerated. There have been reports that describe how the esterification of sterols (stanols) to a fatty acid or edible oil produces a sterol ester (also called a stanol) with improved micelle solubility characteristics. For example, when sitostanol is esterified to an edible oil such as rapeseed oil, a wax-like mixture of fatty acid esters with excellent lipid solubility results. These sterol esters are conveniently incorporated into food products such as margarine.

U.S. Patent Nos. 6,387,411 and 6,376,481 describe sterol/stanol particles in the range of 10-150 microns and 10-40 microns to be most effective when ingested.

Conventionally, plant sterols have been incorporated into food products by melting a sterol or stanol, incorporating it into an oil phase, and blending the oil phase with other components to result in a plant sterol-containing food product. However, plant sterols generally are insoluble and have high melting points (*i.e.*, about 130-180°C), which can result in significant crystallization of the plant sterols within the oil phase of such food products. Such crystallization results in food products with a gritty and unacceptable texture. This gritty texture is especially detectable when the oil/plant sterol phase is incorporated at high levels in the food product. The high melting points and hydrophobic nature of such plant sterols also makes it difficult to blend such plant sterols with an aqueous phase. Furthermore, actual melting of the plant sterol for incorporation into food products is energy intensive.

Attempts have been made to solve these problems using, for example, chemical modification of the plant sterols. For example, esterification of plant sterols generally results in lowered melting temperatures. Thus, such plant sterol esters generally may be

incorporated into food products more readily due to the lower melting points and can provide food products without significant gritty texture.

The mechanism by which plant sterols achieve the effect of lowering serum cholesterol has not been fully elucidated. It is believed that plant sterols interfere with cholesterol absorption by competition-type mechanisms. Cholesterol absorption appears to take place primarily in the proximal third of the small intestine. Cholesterol esters must be converted to their free hydroxyl form by the action of cholesterol esterases before they can be absorbed. The free cholesterol requires bile salts for solubilization and absorption. Bile salts form an aqueous dispersion of micelles in which the cholesterol is solubilized along with phospholipids and hydrolysis products of other dietary lipids. Micelles transport the cholesterol across the hydrophilic barrier (the unstirred water layer) to reach the surface of the intestinal mucosa. At the mucosa, it is thought that the cholesterol dissociates from the micelle and is transported into the mucosa cells by a process which has not yet been fully defined but may include passive exchange diffusion or by protein-mediated transport.

Plant sterols could interfere with cholesterol absorption by the following general mechanisms: (a) competition with cholesterol for absorption into the bile-salt micelles, and/or (b) competition with the transport mechanism into the mucosa cells.

It would be desirable to provide stable, dispersible sterol particles, up to about the 2000 nm size range, which can be readily prepared and formulated in pharmaceutically useful and more convenient, palatable forms for consumption. The present invention satisfies these needs.

SUMMARY OF THE INVENTION

The present invention relates to nanoparticulate active agent compositions comprising at least one sterol and/or stanol, collectively referred to as a "sterol", and novel sterol combinations. The compositions preferably comprise at least one sterol and at least one surface stabilizer adsorbed on or associated with the surface of the one or

more sterol particles. The nanoparticulate sterol particles preferably have an effective average particle size of less than about 2000 nm.

Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate sterol composition of the invention. The pharmaceutical compositions preferably comprise at least one sterol, at least one surface stabilizer, and at least one pharmaceutically acceptable carrier, as well as any desired excipients known to those in the art and formulated into the dosage form desired.

In another aspect of this invention, novel combinations of sterols and at least one other cholesterol lowering agent are described and methods of using the same are taught.

Another aspect of the invention is directed to a nanoparticulate sterol composition having improved pharmacokinetic profiles as compared to conventional microcrystalline sterol formulations, such as improved T_{max}, C_{max}, and/or AUC parameters.

One embodiment of the invention encompasses a sterol stanol composition, wherein the pharmacokinetic profile of the sterol is not affected by the fed or fasted state of a subject ingesting the composition, preferably as defined by C_{max} and AUC guidelines given by the U.S. Food and Drug Administration and/or the corresponding European regulatory agency (EMEA).

In yet another embodiment, the invention encompasses a sterol composition of the invention, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, in particular as defined by C_{max} and AUC guidelines given by the U.S. Food and Drug Administration and the corresponding European regulatory agency (EMEA).

Other embodiments of the invention include, but are not limited to, nanoparticulate sterol compositions which, as compared to conventional non-nanoparticulate formulations of the same sterol, preferably have one or more of the following properties: (1) smaller tablet or other solid dosage form size; (2) smaller doses of drug required to obtain the same pharmacological effect; (3) increased bioavailability; (4) an increased rate of dissolution for the nanoparticulate sterol compositions; and (6) bioadhesive sterol compositions.

This invention further discloses a method of making a nanoparticulate sterol composition according to the invention. Such method comprises contacting at least one sterol with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate sterol composition. The one or more surface stabilizers can be contacted with the sterol before, preferably during, or after size reduction of the sterol.

The present invention is also directed to methods of treatment using the nanoparticulate sterol compositions of the invention for conditions such as hypercholesterolemia, hypertriglyceridemia, coronary heart disease, and peripheral vascular disease (including symptomatic carotid artery disease). In one aspect, the compositions of the invention can be used as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). In another aspect, the compositions can be used as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Markedly elevated levels of serum tryglycerides (*e.g.*, > 2000 mg/dL) may increase the risk of developing pancreatitis. Other diseases that may be directly or indirectly associated with elevated, uncontrolled cholesterol metabolism, *e.g.*, restenosis and Alzheimer's disease, may also be treated with the compositions of this invention. Other methods of treatment using the nanoparticulate sterol compositions of the present invention are known to those of skill in the art.

Such methods comprise administering to a subject a therapeutically effective amount of a nanoparticulate sterol pharmaceutical composition according to the invention.

Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to nanoparticulate active agent compositions comprising at least one sterol and/or stanol, collectively referred to as a "sterol", and novel sterol and/or stanol combinations. Examples of useful sterols include, *e.g.*, sitosterol and phytosterol. The compositions preferably comprise at least one sterol and at least one surface stabilizer adsorbed on or associated with the surface of the sterol particles. The nanoparticulate sterol particles preferably have an effective average particle size of less than about 2000 nm.

As taught in the '684 patent, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition. It was surprisingly discovered that stable nanoparticulate sterol compositions can be made.

A need exists for safer and higher potency sterols. Compositions of nanoparticulate sterols decrease the amount of drug needed and this, in turn, decreases adverse side effects while providing maximum dose response. Additionally, a longer plasma half-life is believed to be associated with nanoparticulate sterol compositions of the invention. Moreover, increasing the duration of effect of the sterol compositions is expected to result in even lower serum cholesterol levels, with a further reduction in dose expected.

In general, the rate of dissolution of a particulate drug can increase with increasing surface area, *e.g.*, decreasing particle size. Consequently, methods of making finely divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions. However, nanoparticulate active agent formulations suitable for administration as a pharmaceutical require formulation of the active ingredient into a colloidal dispersion exhibiting the acceptable nanoparticle size range and the stability to maintain such size range and not agglomerate. Merely increasing surface area by decreasing particle size does not assure success. Further challenges include forming solid dose forms redispersible into the nanoparticle form upon administration to the patient to maintain the benefit of the nanoparticle sterol over the

traditional dosage form.

Advantages of the nanoparticulate sterol compositions of the invention as compared to conventional non-nanoparticulate formulations of the same sterol preferably include, but are not limited to: (1) smaller tablet or other solid dosage form size; (2) smaller doses of drug required to obtain the same pharmacological effect; (3) increased bioavailability; (4) substantially similar pharmacokinetic profiles of the nanoparticulate sterol compositions when administered in the fed versus the fasted state; (5) improved pharmacokinetic profiles; (6) bioequivalency of the nanoparticulate sterol compositions when administered in the fed versus the fasted state; (7) an increased rate of dissolution for the nanoparticulate sterol compositions; (8) bioadhesive sterol compositions; and (9) the nanoparticulate sterol compositions can be used in conjunction with other active agents.

The present invention also includes nanoparticulate sterol compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (*e.g.,* intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized. Exemplary solid dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, or granules. The solid dosage form can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof. A solid dose tablet formulation is preferred.

The preferred method by which the composition of the present invention is used to reduce cholesterol absorption includes the step of mixing the composition with foods and beverages and mixing. The novel food additive is also effective as an additive in

margarine, cooking oils or shortening and preferably fruit and vegetable juices preferably orange or tomato juice for the purpose of reducing serum cholesterol in humans who ingest food products made with the novel composition of this invention.

The present invention is described herein using several definitions, as set forth below and throughout the application.

"About" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which the term is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

"Conventional" or "non-nanoparticulate active agent" shall mean an active agent which is solubilized or which has an effective average particle size of greater than about 2 microns.

"Poorly water soluble drugs" as used herein means those having a solubility of less than about 30 mg/ml, preferably less than about 20 mg/ml, preferably less than about 10 mg/ml, or preferably less than about 1 mg/ml. Such drugs tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation. Moreover, poorly water soluble drugs tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with highly water soluble drug substances.

As used herein with reference to stable sterol particles, "stable" includes, but is not limited to, one or more of the following parameters: (1) that the sterol particles do not appreciably flocculate or agglomerate due to interparticle attractive forces, or otherwise significantly increase in particle size over time; (2) that the physical structure of the sterol particles is not altered over time, such as by conversion from an amorphous phase to crystalline phase; (3) that the sterol particles are chemically stable; and/or (4) where the sterol has not been subject to a heating step at or above the melting point of the sterol in the preparation of the nanoparticles of the invention.

As used herein, the term "sterol" encompasses both sterols and stanols.

"Therapeutically effective amount" as used herein with respect to a drug dosage, shall mean that dosage that provides the specific pharmacological response for which the

drug is administered in a significant number of subjects in need of such treatment. It is emphasized that "therapeutically effective amount," administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a 'therapeutically effective amount' by those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

I. Preferred Characteristics of the Sterol Compositions of the Invention

A. Increased Bioavailability and Lower Dosages

The sterol compositions of the invention preferably exhibit increased bioavailability, at the same dose of the same sterol, require smaller doses, and show longer plasma half-life as compared to prior conventional sterol formulations.

In one aspect of the invention, pharmaceutical sterol compositions have enhanced bioavailability such that the sterol dosage can be reduced, resulting in a decrease in toxicity associated with such sterols. It has been surprisingly found in the present invention that stable compositions of nanoparticulate sterols can be formed that permit therapeutic levels at desirably lower dosage.

Greater bioavailability of the sterol compositions of the invention can enable a smaller solid dosage size. This is particularly significant for patient populations such as the elderly, juvenile, and infant.

B. Improved Pharmacokinetic Profiles

The invention also preferably provides sterol compositions having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the sterol compositions preferably includes, but is not limited to: (1) that the T_{max} of a sterol when assayed in the plasma of a mammalian subject following administration is preferably less than the T_{max} for a conventional, non-nanoparticulate form of the same sterol, administered at the same dosage; (2) that the C_{max}

of a sterol when assayed in the plasma of a mammalian subject following administration is preferably greater than the C_{max} for a conventional, non-nanoparticulate form of the same sterol, administered at the same dosage; and/or (3) that the AUC of a sterol when assayed in the plasma of a mammalian subject following administration, is preferably greater than the AUC for a conventional, non-nanoparticulate form of the same sterol, administered at the same dosage.

The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of a sterol. The compositions can be formulated in any way as described below and as known to those of skill in the art.

A preferred sterol composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same sterol, administered at the same dosage, a T_{max} not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, or not greater than about 10% of the T_{max}, exhibited by the non-nanoparticulate formulation of the same sterol.

A preferred sterol and composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same sterol, administered at the same dosage, a C_{max} which is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 100% greater than the C_{max} exhibited by the non-nanoparticulate formulation of the same sterol.

A preferred sterol composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same sterol, administered at the same dosage, an AUC which is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 100% greater than the AUC exhibited by the non-nanoparticulate formulation of the same sterol.

Any formulation giving the desired pharmacokinetic profile is suitable for administration according to the present methods. Exemplary types of formulations giving such profiles are liquid dispersions, gels, aerosols, ointments, creams, solid dose forms, etc. of a nanoparticulate sterol.

C. The Pharmacokinetic Profiles of the Sterol Compositions of the Invention are not Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

The invention encompasses sterol compositions wherein the pharmacokinetic profile of the sterol is preferably not substantially affected by the fed or fasted state of a subject ingesting the composition, when administered to a human. This means that there is no substantial difference in the quantity of drug absorbed or the rate of drug absorption when the nanoparticulate sterol compositions are administered in the fed versus the fasted state.

The invention also encompasses a sterol composition in which administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state. "Bioequivalency" is preferably established by a 90% Confidence Interval (CI) of between 0.80 and 1.25 for both C_{max} and AUC under U.S. Food and Drug Administration regulatory guidelines, or a 90% CI for AUC of between 0.80 to 1.25, and a 90% CI for C_{max} of between 0.70 to 1.43, under the European EMEA regulatory guidelines (T_{max} is not relevant for bioequivalency determinations under USFDA and EMEA regulatory guidelines).

Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food. This is significant, as with poor subject compliance an increase in the medical condition for which the drug is being prescribed may be observed.

The difference in absorption of the sterol compositions of the invention, when administered in the fed versus the fasted state, preferably is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than

about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

D. Dissolution Profiles of the Sterol Compositions of the Invention

The sterol compositions of the invention preferably have unexpectedly dramatic dissolution profiles. Rapid dissolution of an administered active agent is preferable, as faster dissolution generally leads to faster onset of action and greater bioavailability. To improve the dissolution profile and bioavailability of sterols it would be useful to increase the drug's dissolution so that it could attain a level close to 100%.

The sterol compositions of the invention preferably have a dissolution profile in which within about 5 minutes at least about 20% of the composition is dissolved. In other embodiments of the invention, at least about 30% or about 40% of the sterol composition is dissolved within about 5 minutes. In yet other embodiments of the invention, preferably at least about 40%, about 50%, about 60%, about 70%, or about 80% of the sterol composition is dissolved within about 10 minutes. Finally, in another embodiment of the invention, preferably at least about 70%, about 80%, about 90%, or about 100% of the sterol composition is dissolved within about 20 minutes.

Dissolution is preferably measured in a medium which is discriminating. Such a dissolution medium will produce two very different dissolution curves for two products having very different dissolution profiles in gastric juices; *i.e.*, the dissolution medium is predictive of *in vivo* dissolution of a composition. An exemplary dissolution medium is an aqueous medium containing the surfactant sodium lauryl sulfate at 0.025 M. Determination of the amount dissolved can be carried out by spectrophotometry. The rotating blade method (European Pharmacopoeia) can be used to measure dissolution.

E. Redispersibility Profiles of the Sterol Compositions of the Invention

An additional feature of the sterol compositions of the invention is that the compositions preferably redisperse such that the effective average particle size of the redispersed sterol particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate sterol compositions of the invention did not redisperse to a substantially nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating the sterol into a nanoparticulate particle size.

This is because nanoparticulate active agent compositions benefit from the small particle size of the active agent; if the active agent does not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated active agent particles are formed, owing to the extremely high surface free energy of the nanoparticulate system and the thermodynamic driving force to achieve an overall reduction in free energy. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall well below that observed with the liquid dispersion form of the nanoparticulate active agent.

Moreover, the nanoparticulate sterol compositions of the invention preferably exhibit dramatic redispersion of the nanoparticulate sterol particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution/redispersion in a biorelevant aqueous media such that the effective average particle size of the redispersed sterol particles is less than about 2 microns. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength.

Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small

intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1 M while fasted state intestinal fluid has an ionic strength of about 0.14. *See e.g.*, Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," *Pharm. Res., 14* (4): 497-502 (1997).

It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (*i.e.*, weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, *etc.*

Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 M HCl or less, about 0.01 M HCl or less, about 0.001 M HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

Electrolyte concentrations of 0.001 M HCl, 0.01 M HCl, and 0.1 M HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 M HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts + sodium, potassium and calcium salts of chloride, acetic acid/acetate salts + sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts +

sodium, potassium and calcium salts of chloride, and citric acid/citrate salts + sodium, potassium and calcium salts of chloride.

In other embodiments of the invention, the redispersed sterol particles of the invention (redispersed in an aqueous, biorelevant, or any other suitable media) have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the sterol particles have a particle size of less than the effective average, by weight, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, *etc.*, when measured by the above-noted techniques. Preferably, at least about 70%, about 90%, about 95%, or about 99% of the sterol particles have a particle size of less than the effective average, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, 1700 nm, *etc.*

Redispersibility can be tested using any suitable means known in the art. *See e.g.*, the example sections of U.S. Patent No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate."

F. Bioadhesive Sterol Compositions

Bioadhesive sterol compositions of the invention comprise at least one cationic surface stabilizer, which are described in more detail below. Bioadhesive formulations of sterols exhibit exceptional bioadhesion to biological surfaces, such as mucous. The term bioadhesion refers to any attractive interaction between two biological surfaces or

between a biological and a synthetic surface. In the case of bioadhesive nanoparticulate sterol compositions, the term bioadhesion is used to describe the adhesion between the nanoparticulate sterol compositions and a biological substrate (*i.e.* gastrointestinal mucin, lung tissue, nasal mucosa, *etc.*). *See e.g.*, U.S. Patent No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers," which is specifically incorporated by reference.

There are basically two mechanisms which may be responsible for the bioadhesion phenomena: mechanical or physical interactions and chemical interactions. The first of these, mechanical or physical mechanisms, involves the physical interlocking or interpenetration between a bioadhesive entity and the receptor tissue, resulting from a good wetting of the bioadhesive surface, swelling of the bioadhesive polymer, penetration of the bioadhesive entity into a crevice of the tissue surface, or interpenetration of bioadhesive composition chains with those of the mucous or other such related tissues. The second possible mechanism of bioadhesion incorporates forces such as ionic attraction, dipolar forces, van der Waals interactions, and hydrogen bonds. It is this form of bioadhesion which is primarily responsible for the bioadhesive properties of the nanoparticulate sterol compositions of the invention. However, physical and mechanical interactions may also play a secondary role in the bioadhesion of such nanoparticulate compositions.

The bioadhesive sterol compositions of the invention are useful in any situation in which it is desirable to apply the compositions to a biological surface. The bioadhesive sterol compositions coat the targeted surface in a continuous and uniform film which is invisible to the naked human eye.

A bioadhesive sterol composition slows the transit of the composition, and some sterol particles would also most likely adhere to tissue other than the mucous cells and therefore give a prolonged exposure to the sterol, thereby increasing absorption and the bioavailability of the administered dosage.

G. Sterol Compositions Used in Conjunction with Other Active Agents

The sterol compositions of the invention can additionally comprise one or more non-sterol compounds useful: (1) in treating conditions such as dyslipidemia, hyperlipidemia, hypercholesterolemia, cardiovascular disorders, hypertriglyceridemia, coronary heart disease, and peripheral vascular disease (including symptomatic carotid artery disease), or related conditions; (2) as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and/or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb); (3) as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia); (4) in treating pancreatitis; (5) in treating restenosis; and/or (6) in treating Alzheimer's disease.

Exemplary non-sterol compositions useful in the invention include, but are not limited to, cholesterol lowering agents, polycosanols, alkanoyl L-carnitines, antihypertensives, and/or statins.

Useful cholesterol lowering agents are well known to those of skill in the art and include, but are not limited to, ACE inhibitors, nicotinic acid, niacin, bile acid sequestrants, fibrates, vitamins, fatty acid derivatives such as fish oil, long chain plant extract alcohols such as policosinol, ezetimibe, and celluloses.

Useful polycosanols include, but are not limited to, triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, tetracontanol, or natural products or extracts from natural products containing such compounds.

Useful alkanoyl L-carnitines include, but are not limited to, acetyl L-carnitine, propionyl L-carnitine, butyryl L-carnitine, valeryl L-carnitine, and isovaleryl L-carnitine, or a pharmacologically acceptable salt thereof.

Useful antihypertensives include, but are not limited to diuretics ("water pills"), beta blockers, alpha blockers, alpha-beta blockers, sympathetic nerve inhibitors, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, angiotensin

receptor blockers (formal medical name angiotensin-2-receptor antagonists, known as "sartans" for short).

Useful statins include, but are not limited to, atorvastatin (Lipitor®) (U.S. Patent No. 4,681,893) and other 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivatives as disclosed in U.S. Patent No. 4,647,576); fluvastatin (Lescol®) (U.S. Patent No. 5,354,772); lovastatin (U.S. Patent No. 4,231,938); pravastatin (U.S. Patent No. 4,346,227); simvastatin (U.S. Patent No. 4,444,784); velostatin; fluindostatin (Sandoz XU-62-320); pyrazole analogs of mevalonolactone derivatives, as disclosed in PCT application WO 86/03488; rivastatin and other pyridyldihydroxyheptenoic acids, as disclosed in European Patent 491226A; Searle's SC-45355 (a 3-substituted pentanedioic acid derivative); dichloroacetate; imidazole analogs of mevalonolactone, as disclosed in PCT application WO 86/07054; 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives, as disclosed in French Patent No. 2,596,393; 2,3-di-substituted pyrrole, furan, and thiophene derivatives, as disclosed in European Patent Application No. 0221025; naphthyl analogs of mevalonolactone, as disclosed in U.S. Patent No. 4,686,237; octahydronaphthalenes, such as those disclosed in U.S. Patent No. 4,499,289; keto analogs of mevinolin (lovastatin), as disclosed in European Patent Application No. 0,142,146 A2; phosphinic acid compounds; as well as other HMG CoA reductase inhibitors.

Such additional compounds can have a conventional non-nanoparticulate particle size, *i.e.*, an effective average particle size greater than about 2 microns, or such additional compounds can be formulated into a nanoparticulate particle size, *i.e.*, an effective average particle size of less than about 2 microns. If such one or more non-sterol compounds have a nanoparticulate particle size, then preferably such non-sterol compounds are poorly soluble in at least one liquid media (poorly soluble as defined in the "Definitions" section, above), and have at least one surface stabilizer adsorbed on or associated with the surface of the non-sterol compound. The one or more surface stabilizers utilized in the composition of the non-sterol compound can be the same as or

different from the one or more surface stabilizers utilized in the sterol composition. A description of surface stabilizers useful in the invention is provided below.

II. Compositions

The present invention is directed to nanoparticulate active agent compositions comprising at least one sterol, and novel sterol combinations. The compositions preferably comprise: (1) at least one sterol or a salt thereof; and (2) at least one surface stabilizer adsorbed on, or associated with, the surface of the sterol. The nanoparticulate sterol particles preferably have an effective average particle size of less than about 2000 nm. In another aspect of this invention, novel combinations of sterols and other cholesterol lowering agents are described and methods of using the same are taught.

The present invention also includes nanoparticulate sterol compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for various routes of administration including but not limited to, oral, rectal, ocular, and parenteral injection (*e.g.*, intravenous, intramuscular, or subcutaneous), oral administration in solid (the preferred route), liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (e.g., in powder, ointment or drop form), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

A. Sterol Particles

As used herein the term "sterol" includes both stanols and sterols, or a salt thereof, preferably having a solubility in water of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, or more preferably less than about 1 mg/ml.

The one or more sterol particles, or salt thereof, can be in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

The term "stanol" is well known to those skilled in the art and generally refers to compounds having a saturated perhydrocyclopentanophenanthrene ring system and having one or more OH substituents, examples of which include, but are not limited to,

campestanol, sitostanol, which also known as beta-sitostanol and stigmastanol, coprostanol, cholestanol and the like.

"Stanols" as used herein mean plant stanol esters, a food ingredient that can help reduce LDL cholesterol. Plant stanols are derived from naturally occurring substances in plants by techniques known to those in the art. Stanols are frequently combined with a small amount of canola oil to form stanol esters, producing an ingredient that can be used in a wide variety of foods and in combination with the compositions of this invention.

Plant sterols and stanols are not produced by animals or the human body. Plant sterols and stanols are natural substances found in wood pulp, leaves, nuts, vegetable oils, corn, rice, and some other plants. The major plant sterol is sitosterol (approx. 80%). Others present in the diet include campesterol and stigmasterol, and trace amounts of plant stanols such as sitostanol. Plant sterols and stanols are similar in structure to cholesterol. The difference is the presence of a methyl or ethyl group in their side chains. This difference means that, in comparison to cholesterol, plant sterol and stanols are not absorbed, or are minimally absorbed.

As disclosed in U.S. Pat. Nos. 5,244,877, 5,502,045 and 5,578,334, various sterols, in particular beta-sitosterol, are known to have cholesterol-lowering properties. The consumption of beta-sitosterol is known to reduce cholesterol levels in the blood stream. Presently, due to its handling and storage properties, beta-sitosterol is incorporated in foods during its formulation, or while it is being manufactured. While this is effective in producing foods with beneficial effects, the consumer is limited to those foods in which manufacturers incorporate beta-sitosterol.

Sterols are typically derived from agricultural sources, such as corn, soy-based, and pine tree mixtures. The present invention also contemplates esters of sterols, called "stanols", through the reaction of the sterol with the suitable acid. Suitable acids include saturated, unsaturated, and polyunsaturated acids. Suitable acids include but are not limited to, stearic, butyric, lauric, palmitic, oleic, linoleic, linolenic, docohexanoic acid, and the like. Suitable methods for preparing these esters are well known in the art. *See*

e.g., U.S. Pat. Nos. 5,502,045 and 5,723,747, the contents of which are incorporated herein by reference.

High LDL cholesterol is usually first treated with exercise, weight loss in obese individuals, and a diet low in cholesterol and saturated fats. When these measures fail, cholesterol-lowering medications, such as a sterol, can be added. The National Cholesterol Education Program (NCEP) has published treatment guidelines for use of sterols. These treatment guidelines take into account the level of LDL cholesterol as well as the presence of other risk factors such as diabetes, hypertension, cigarette smoking, low HDL cholesterol level, and family history of early coronary heart disease.

B. Surface Stabilizers

Surface stabilizers especially useful herein physically adhere on or associate with the surface of the nanoparticulate sterol but do not chemically react with the sterol particles or itself. Preferably, individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

The choice of a surface stabilizer for a sterol is non-trivial and required extensive experimentation to realize a desirable formulation for the active ingredient's therapeutic effect desired. For example, the effectiveness of using of a particular stabilizer with an active ingredient is unpredictable because the stabilizer among other factors, will affect dissolution and pharmacokinetic profiles for a sterol. Accordingly, the present invention is directed to the surprising discovery that stable, therapeutically useful, nanoparticulate sterol compositions can be made.

Combinations of more than one surface stabilizer can preferably be used in the invention. Useful surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Preferred surface stabilizers include nonionic, anionic, cationic, and zwitterionic surfactants.

Representative examples of surface stabilizers include hydroxypropylmethylcellulose (anionic), hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate (anionic), gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens® such as *e.g.*, Tween 20® and Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (*e.g.*, Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methyl cellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (*e.g.*, Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (*e.g.*, Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), Triton X-200®, which is an alkyl aryl polyether sulfonate (Dow Chemical); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-lOG® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)\text{-}CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-

thioglucopyranoside; PEG-derivatized phospholipid, PEG- derivatized cholesterol, PEG-derivatized cholesterol derivative, PEG- derivatized vitamin A, PEG- derivatized vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like such as Plasdone® S630 in a 60:40 ratio of the pyrrolidone and vinyl acetate.

More examples of useful surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexadecyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl $(ethenoxy)_4$ ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride,

dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry,* (Marcel Dekker, 1990).

Nonpolymeric surface stabilizers are any nonpolymeric compound, such benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a

secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

(i) none of R_1-R_4 are CH_3;

(ii) one of R_1-R_4 is CH_3;

(iii) three of R_1-R_4 are CH_3;

(iv) all of R_1-R_4 are CH_3;

(v) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of seven carbon atoms or less;

(vi) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of nineteen carbon atoms or more;

(vii) two of R_1-R_4 are CH_3 and one of R_1-R_4 is the group $C_6H_5(CH_2)_n$, where $n>1$;

(viii) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one heteroatom;

(ix) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one halogen;

(x) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one cyclic fragment;

(xi) two of R_1-R_4 are CH_3 and one of R_1-R_4 is a phenyl ring; or

(xii) two of R_1-R_4 are CH_3 and two of R_1-R_4 are purely aliphatic fragments.

Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium

POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference.

The surface stabilizers are commercially available and/or can be prepared by techniques known in the art.

C. Other Pharmaceutical Excipients

Pharmaceutical compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients d
depending upon the route of administration and the dosage form desired. Such excipients are known in the art.

Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acsulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

D. Nanoparticulate Sterol Particle Size

The compositions of the invention contain sterol nanoparticles, such as sitosterol and/or phytosterol nanoparticles, which have an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns). In a preferred embodiment of the invention, the sterol nanoparticles have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the sterol particles have a particle size less than the effective average, by weight, *i.e.*, less than about 2000 nm, about 1900 nm, about 1800 nm, *etc.*, when measured by the above-noted techniques. Preferably, at least about 70%, about 90%, about 95%, or about 99% of the sterol particles have a particle size less than the effective average, *i.e.*, less than about 2000 nm, about 1900 nm, about 1800 nm, *etc.*

In the present invention, the value for D50 of a nanoparticulate sterol composition is the particle size below which 50% of the sterol particles fall, by weight. Similarly, D90 is the particle size below which 90% of the sterol/stanol particles fall, by weight.

E. Concentration of Nanoparticulate Sterol and Surface Stabilizers

The relative amounts of at least one sterol and one or more surface stabilizers can vary widely. The optimal amount of the individual components depends, for example, upon one or more of the physical and chemical attributes of the particular sterol selected and surface stabilizer(s) selected, such as the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer, *etc.*

Preferably, the concentration of the at least one sterol can vary from about 99.5% to about 0.001%, preferably from about 95% to about 0.1%, preferably from about 90% to about 0.5%, by weight, based on the total combined weight of the sterol and at least one surface stabilizer, not including other excipients. Higher concentrations of the active ingredient are generally preferred from a dose and cost efficiency standpoint.

Preferably, the concentration of the at least one surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the sterol and at least one surface stabilizer, not including other excipients.

Exemplary useful ratios of active ingredient to stabilizers herein are preferably about 1:1, preferably about 2:1, preferably about 3:1, preferably about 4:1, preferably about 5:1, preferably about 6:1, preferably about 7:1, preferably about 8:1, and preferably about 10:1, by weight, based on the total combined dry weight of the sterol and at least one surface stabilizer, not including other excipients.

III. Methods of Making Nanoparticulate Sterol Compositions

The nanoparticulate sterol compositions can be made using any suitable method known in the art such as, for example, milling, homogenization, or precipitation techniques. Exemplary methods of making nanoparticulate compositions are described in the '684 patent. Methods of making nanoparticulate compositions are also described in U.S. Patent No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,665,331 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,662,883 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,560,932 for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Patent No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Patent No. 5,534,270 for

"Method of Preparing Stable Drug Nanoparticles;" U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Patent No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

The resultant nanoparticulate sterol compositions or dispersions can be utilized in solid or liquid dosage formulations, such as liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release and controlled release formulations, *etc.* Solid dose forms of the dispersions of novel sterol formulations according to the present invention can be made as described in U.S. Patent No. 6,375,986.

A. Milling to Obtain Nanoparticulate Sterol Dispersions

Milling a sterol to obtain a nanoparticulate sterol dispersion comprises dispersing sterol particles in a liquid dispersion medium in which the sterol is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the sterol to the desired effective average particle size. The dispersion medium can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol.

The sterol particles can be reduced in size preferably in the presence of at least one surface stabilizer. Alternatively, the sterol particles can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the sterol/surface stabilizer composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

B. Precipitation to Obtain Nanoparticulate Sterol Compositions

Another method of forming the desired nanoparticulate sterol composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble

active agents in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving a sterol in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

C. Homogenization to Obtain Sterol Nanoparticulate Compositions

Exemplary homogenization methods of preparing active agent nanoparticulate compositions are described in U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." Such a method comprises dispersing sterol particles in a liquid dispersion medium in which the sterol is poorly soluble, followed by subjecting the dispersion to homogenization to reduce the particle size of the sterol to the desired effective average particle size. The sterol particles are preferably reduced in size in the presence of at least one surface stabilizer. Alternatively, the sterol particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the sterol/surface stabilizer composition before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

IV. Methods of Using Sterol Compositions of the Current Invention

The sterol compositions of the present invention can be administered to a subject via any conventional means including, but not limited to, preferably orally, rectally, ocularly, parenterally (*e.g.*, intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (*e.g.*, powders, ointments or drops), or as a buccal or nasal spray. As used herein, the term "subject" is used to mean an

animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

The present invention provides a method of prolonging plasma levels of a sterol in a subject while achieving the desired therapeutic effect. In one aspect, such a method comprises orally administering to a subject an effective amount of a composition of this invention comprising a sterol.

In one aspect, the compositions of the invention are useful in treating conditions that may be directly or indirectly associated with elevated and/or uncontrolled cholesterol metabolism as described herein and known to those in the art.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

The nanoparticulate sterol compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can also be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

Solid dosage forms for oral administration are preferred and include, but are not limited to; capsules, tablets, pills, powders, caplets, and granules. In such solid dosage forms, the active agent (*i.e.*, the composition of this invention) is admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate

or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Liquid dosage forms for oral administration include pharmaceutically acceptable dispersions, emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active agent, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

The effective amounts of the sterol compositions of the invention can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of sterol in the nanoparticulate compositions of the invention may be varied to obtain an amount of sterol that is effective to obtain a desired therapeutic response for a particular composition, method of administration, and the condition to be treated. The selected dosage level therefore depends upon the desired therapeutic effect, the route of

administration, the potency of the administered sterol, the desired duration of treatment, and other factors.

Dosage unit compositions may contain amounts of submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

V. Sterol Combinations

Sterol compositions of the present invention are also particularly useful when given pursuant to the method of this invention in combination with a therapeutically effective amount of at least one other non-sterol active agent useful: (1) in treating conditions such as dyslipidemia, hyperlipidemia, hypercholesterolemia, cardiovascular disorders, hypertriglyceridemia, coronary heart disease, and peripheral vascular disease (including symptomatic carotid artery disease), or related conditions; (2) as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and/or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb); (3) as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia); (4) in treating pancreatitis; (5) in treating restenosis; and/or (6) in treating Alzheimer's disease.

Exemplary non-sterol compositions useful in the invention include, *e.g.*, cholesterol lowering agents, polycosanols, alkanoyl L-carnitines, antihypertensives, and/or statins.

Useful cholesterol lowering agents are well known to those of skill in the art and include, but are not limited to, ACE inhibitors, nicotinic acid, niacin, bile acid sequestrants, fibrates, vitamins, fatty acid derivatives such as fish oil, long chain plant extract alcohols such as policosinol, ezetimibe, and celluloses.

Useful polycosanols include, but are not limited to, triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, tetracontanol, or natural products or extracts from natural products containing such compounds.

Useful alkanoyl L-carnitines include, but are not limited to, acetyl L-carnitine, propionyl L-carnitine, butyryl L-carnitine, valeryl L-carnitine, and isovaleryl L-carnitine, or a pharmacologically acceptable salt thereof.

Useful antihypertensives include, but are not limited to diuretics ("water pills"), beta blockers, alpha blockers, alpha-beta blockers, sympathetic nerve inhibitors, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, angiotensin receptor blockers (formal medical name angiotensin-2-receptor antagonists, known as "sartans" for short).

Useful statins include, but are not limited to, atorvastatin (Lipitor®) (U.S. Patent No. 4,681,893) and other 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivatives as disclosed in U.S. Patent No. 4,647,576); fluvastatin (Lescol®) (U.S. Patent No. 5,354,772); lovastatin (U.S. Patent No. 4,231,938); pravastatin (U.S. Patent No. 4,346,227); simvastatin (U.S. Patent No. 4,444,784); velostatin; fluindostatin (Sandoz XU-62-320); pyrazole analogs of mevalonolactone derivatives, as disclosed in PCT application WO 86/03488; rivastatin and other pyridyldihydroxyheptenoic acids, as disclosed in European Patent 491226A; Searle's SC-45355 (a 3-substituted pentanedioic acid derivative); dichloroacetate; imidazole analogs of mevalonolactone, as disclosed in PCT application WO 86/07054; 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives, as disclosed in French Patent No. 2,596,393; 2,3-di-substituted pyrrole, furan, and thiophene derivatives, as disclosed in European Patent Application No. 0221025; naphthyl analogs of mevalonolactone, as disclosed in U.S. Patent No. 4,686,237; octahydronaphthalenes, such as those disclosed in U.S. Patent No. 4,499,289; keto

analogs of mevinolin (lovastatin), as disclosed in European Patent Application No. 0,142,146 A2; phosphinic acid compounds; as well as other HMG CoA reductase inhibitors.

* * * * *

The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. Throughout the specification, any and all references to a publicly available document, including a U.S. patent, are specifically incorporated by reference.

In the examples that follow, the particle sizes were measured using a Horiba LA-910 Laser Scattering Particle Size Distribution Analyzer (Horiba Instruments, Irvine, CA). The particle mean and D_{90} (which is the size below which 90% of the distribution is located) are obtained from a weight distribution. All formulations are given in weight % (w/w).

Several of the formulations in the examples that follow were also investigated using a light microscope.

Example 1

The purpose of this example was to identify formulations that would produce stable nanoparticulate dispersions of phytosterol. Phytosterol is a plant sterol, found in abundance in fat-soluble fractions of plants. Phytosterol, sold under the trade name Reducol™, can be commercially obtained from Novartis Consumer Health SA.

Arriving at a formulation that results in a stable dispersion having a small particle size is nontrivial and requires extensive experimentation. Two formulations meeting this criteria were prepared as follows.

5% (w/w) phytosterol and 1% (w/w) surface stabilizer, identified in Table 1, were each milled at 10 °C for 1.5 to 2 hours in a DYNO®-Mill KDL (Willy A. Bachofen

AG, Maschinenfabrik, Basel, Switzerland) using a 500 μm milling media of type Polymill® 500.

All particle sizes were measured using a Horiba LA-910 Laser Scattering Particle Size Distribution Analyzer (Horiba Instruments, Irvine, CA). The phytosterol particle mean and D_{90} were obtained from a weight distribution. All formulations are given in weight % (w/w).

Table 1
Particle size of 5% Phytosterol at 1% stabilizer

	Size at harvest		Size after 2 weeks at 25 °C		
Stabilizer	**Mean (nm)**	**D_{90} (nm)**	**Mean (nm)**	**D_{90} (nm)**	**1 min sonication**
1.0% Pluronic® F108	380	622	752	472	N
(Poloxamer 338)	272	405	225	351	Y
1.0% Tween® 80	119	187	139	187	N
(Polysorbate 80)	119	187	139	187	Y

Both formulations exhibit acceptable stability criteria, while the formulation containing Tween® 80 appears to perform the best.

Example 2

The purpose of this example was to show the feasibility of using a phytosterol nanoparticulate dispersion as a food additive.

A phytosterol dispersion, prepared as in Example 1, was added to orange juice supernatant at the final concentration of 1% (w/w) phytosterol and 0.15% (w/w) Tween® 80. Orange juice supernatant was used simply to facilitate the particle size analysis, which otherwise would have been obscured by the orange pulp. The supernatant was produced by centrifugation of commercially available orange juice.

Shown below in Table 2 is the stability at room temperature of a phytosterol dispersion at a total concentration of 1% (w/w) phytosterol and 0.15% (w/w) Tween® 80 in orange juice supernatant.

Table 2
Stability of a Nanoparticulate Phytosterol Composition in Orange Juice Supernatant

Time (days)	Mean (nm)	D90 (nm)	1 min sonication
0	181	242	N
	177	236	Y
1	166	220	N
	166	219	Y
7	194	264	N
	186	253	Y

The absence of aggregation over the evaluated time period indicates that the formulation is compatible with a fruit juice such as orange juice. This will promote the content uniformity (*i.e.*, prevent the phytosterol particles from sedimenting to the bottom) as well as to eliminate a gritty mouth feel.

* * * *

It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

We claim:

1. A composition comprising:

(a) particles of at least one sterol or a salt thereof, wherein the sterol particles have an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer.

2. The composition of claim 1, wherein the sterol is selected from the group consisting of plant sterols, plant sterol esters, fish oil, sitosterol, sitostanol, phytosterol, campestanol, stigmasterol, coprostanol, cholestanol, and beta-sitosterol.

3. The composition of claim 1 or claim 2, wherein the sterol is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

4. The composition of any one of claims 1-3, wherein the effective average particle size of the sterol particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

5. The composition of any one of claims 1-4, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

6. The composition of any one of claims 1-5 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

7. The composition of any one of claims 1-6, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

8. The composition of any one of claims 1-7, wherein the at least one sterol or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the sterol or a salt thereof and at least one surface stabilizer, not including other excipients.

9. The composition of any one of claims 1-8, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the sterol or a salt thereof and at least one surface stabilizer, not including other excipients.

10. The composition of any one of claims 1-9, comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

11. The composition of any one of claims 1-10, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

12. The composition of claim 11, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

13. The composition of claim 11, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

14. The composition of claim 11, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl $(ethenoxy)_4$ ammonium chloride, lauryl dimethyl $(ethenoxy)_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl

benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

15. The composition of any of claims 11, 13, or 14, wherein the composition is bioadhesive.

16. The composition of any one of claims 1-15, comprising Pluronic® F108 or Tween® 80 as surface stabilizers.

17. The composition of any one of claims 1-16, wherein the T_{max} of the sterol, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a conventional, non-nanoparticulate form of the same sterol, administered at the same dosage.

18. The composition of claim 17, wherein the T_{max} is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%,

and not greater than about 10% of the T_{max}, exhibited by a non-nanoparticulate formulation of the same sterol, administered at the same dosage.

19. The composition of any one of claims 1-18, wherein the C_{max} of the sterol, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{max} for a conventional, non-nanoparticulate form of the same sterol, administered at the same dosage.

20. The composition of claim 19, wherein the C_{max} is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the C_{max} exhibited by a non-nanoparticulate formulation of the same sterol, administered at the same dosage.

21. The composition of any one of claims 1-20, wherein the AUC of the sterol, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of the same sterol, administered at the same dosage.

22. The composition of claim 21, wherein the AUC is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the AUC exhibited by a non-nanoparticulate formulation of the same sterol, administered at the same dosage.

23. The composition of any one of claims 1-22 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

24. The composition of claim 23, wherein the difference in absorption of the sterol composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

25. The composition of any one of claims 1-24, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

26. The composition of claim 25, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human.

27. The composition of claim 25, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max}, when administered to a human.

28. The composition of any one of claims 1-27, wherein within about 5 minutes at least about 20% of the composition is dissolved, wherein dissolution is measured in a media which is discriminating and wherein the rotating blade method (European Pharmacopoeia) is used to measure dissolution.

29. The composition of claim 28, in which at least about 30% or at least about 40% of the composition is dissolved within about 5 minutes.

30. The composition of claim 28, wherein upon redispersion the sterol particles have an effective average particle size of less than about 2 microns.

31. The composition of any one of claims 1-30, wherein within about 10 minutes at least about 40% of the composition is dissolved, wherein dissolution is measured in a media which is discriminating and wherein the rotating blade method (European Pharmacopoeia) is used to measure dissolution.

32. The composition of claim 31, wherein at least about 50%, about 60%, about 70%, or about 80% of the composition is dissolved within about 10 minutes.

33. The composition of claim 31, wherein upon redispersion the sterol particles have an effective average particle size of less than about 2 microns.

34. The composition of any one of claims 1-33, wherein within about 20 minutes at least about 70% of the composition is dissolved, wherein dissolution is measured in a media which is discriminating and wherein the rotating blade method (European Pharmacopoeia) is used to measure dissolution.

35. The composition of claim 34, wherein at least about 80%, about 90%, or about 100% of the composition is dissolved within about 20 minutes.

36. The composition of claim 34, wherein upon redispersion the sterol particles have an effective average particle size of less than about 2 microns.

37. The composition of any one of claims 1-36, additionally comprising one or more non-sterol active agents selected from the group consisting of:

(a) an active agent useful in treating dyslipidemia;

(b) an active agent useful in treating hyperlipidemia;

(c) an active agent useful in treating hypercholesterolemia;

(d) an active agent useful in treating cardiovascular disorders;

(e) an active agent useful in treating hypertriglyceridemia;

(f) an active agent useful in treating coronary heart disease;

(g) an active agent useful in treating peripheral vascular disease;

(h) an active agent useful as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and/or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb);

(i) an active agent useful as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia);

(j) an active agent useful in treating pancreatitis;

(k) an active agent useful in treating restenosis; and

(l) an active agent useful in treating Alzheimer's disease.

38. The composition of any one of claims 1-37, additionally comprising one or more non-sterol active agents selected from the group consisting of cholesterol lowering agents, polycosanols, alkanoyl L-carnitines, antihypertensives, and statins.

39. The composition of claim 38, wherein the cholesterol lowering agent is selected from the group consisting of ACE inhibitors, nicotinic acid, niacin, bile acid sequestrants, fibrates, vitamins, fatty acid derivatives, long chain plant extract alcohols, ezetimibe, and celluloses.

40. The composition of claim 38, wherein the polycosanol is selected from the group consisting of (1) triacontanol, (2) hexacontanol, (3) ecocosanol, (4) hexacosanol, (5) tetracosanol, (6) dotriacontanol, (7) tetracontanol, (8) natural products comprising triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, or tetracontanol; and (9) extracts of natural products comprising triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, or tetracontanol.

41. The composition of claim 38, wherein the antihypertensive is selected from the group consisting of diuretics, beta blockers, alpha blockers, alpha-beta blockers, sympathetic nerve inhibitors, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin receptor blockers.

42. The composition of claim 38, wherein the statin is selected from the group consisting of atorvastatin; a 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivative other than atorvastatin; lovastatin; a keto analog of mevinolin other than lovastatin; pravastatin; simvastatin; velostatin; fluindostatin; pyrazole analogs of mevalonolactone derivatives; rivastatin; a pyridyldihydroxyheptenoic acid other than rivastatin; SC-45355; dichloroacetate; imidazole analogs of mevalonolactone; 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives; 2,3-di-substituted pyrrole derivatives; 2,3-di-substituted furan derivatives; 2,3-di-substituted thiophene derivatives; naphthyl analogs of mevalonolactone; octahydronaphthalenes; and phosphinic acid compounds.

43. The composition according to any one of claims 37-42, wherein at least one of the non-sterol compounds has an effective average particle size of greater than about 2 microns.

44. The composition according to any one of claims 37-42, wherein at least one of the non-sterol compounds has an effective average particle size of less than about 2 microns.

45. The composition of any one of claims 1-44, wherein upon administration the composition redisperses such that the sterol particles have an effective average particle size selected from the group consisting of less than about 2000 nm, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than

about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

46. The composition of any one of claims 1-44, wherein the composition redisperses in a biorelevant media such that the sterol particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

47. A method of making a sterol composition comprising contacting particles of at least one sterol or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a sterol composition having an effective average particle size of less than about 2000 nm.

48. The method of claim 47, wherein said contacting comprises grinding.

49. The method of claim 48, wherein said grinding comprises wet grinding.

50. The method of claim 47, wherein said contacting comprises homogenizing.

51. The method of claim 47, wherein said contacting comprises:

(a) dissolving the particles of a sterol or a salt thereof in a solvent;

(b) adding the resulting sterol solution to a solution comprising at least one surface stabilizer; and

(c) precipitating the solubilized sterol having at least one surface stabilizer adsorbed on the surface thereof by the addition thereto of a non-solvent.

52. The method of any one of claims 47-51, wherein the sterol is selected from the group consisting of plant sterols, plant sterol esters, fish oil, sitosterol, sitostanol, phytosterol, campestanol, stigmasterol, coprostanol, cholestanol, and beta-sitosterol.

53. The method of any one of claims 47-52, wherein the sterol or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

54. The method of any one of claims 47-53, wherein the effective average particle size of the sterol particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1000 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

55. The method of any one of claims 47-54, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

56. The method of any one of claims 47-55, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

57. The method of any one of claims 47-56, wherein the sterol or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the sterol or a salt thereof and at least one surface stabilizer, not including other excipients.

58. The method of any one of claims 47-57, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the sterol or a salt thereof and at least one surface stabilizer, not including other excipients.

59. The method of any one of claims 47-58, comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

60. The method of any one of claims 47-59, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

61. The method of claim 60, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters,

polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

62. The method of claim 60, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

63. The method of claim 60, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium

chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

64. The method of any of claims 60, 62, or 63, wherein the composition is bioadhesive.

65. The method of any one of claims 47-64, comprising Pluronic® F108 or Tween® 80 as surface stabilizers.

66. A method of treating a subject in need comprising administering to the subject an effective amount of a composition comprising:

(a) particles of a sterol or a salt thereof, wherein the sterol particles have an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer associated with the surface of the sterol particles.

67. The method of claim 66, wherein the sterol is selected from the group consisting of plant sterols, plant sterol esters, fish oil, sitosterol, sitostanol, phytosterol, campestanol, stigmasterol, coprostanol, cholestanol, and beta-sitosterol.

68. The method of claim 66 or claim 67, wherein the sterol or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

69. The method of any one of claims 66-68, wherein the effective average particle size of the sterol particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm,

less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

70. The method of any one of claims 66-69, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

71. The method of any one of claims 66-70, wherein the composition is a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

72. The method of any one of claims 66-71, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

73. The method of any one of claims 66-72, wherein the sterol or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the sterol or a salt thereof and at least one surface stabilizer, not including other excipients.

74. The method of any one of claims 66-73, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about

10% to about 99.5% by weight, based on the total combined dry weight of the sterol or a salt thereof and at least one surface stabilizer, not including other excipients.

75. The method of any one of claims 66-74, comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

76. The method of any one of claims 66-75, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

77. The method of claim 76, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-

methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

78. The method of claim 76, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

79. The method of claim 76, wherein the surface stabilizer is selected from the group consisting of benzalkonium chloride, polymethylmethacrylate trimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, cationic lipids, sulfonium compounds, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl $(ethenoxy)_4$ ammonium chloride, lauryl dimethyl $(ethenoxy)_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride,

N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

80. The method of any of claims 76, 78, or 79, wherein the composition is bioadhesive.

81. The method of any one of claims 66-80, comprising Pluronic® F108 or Tween® 80 as surface stabilizers.

82. The method of any one of claims 66-81, wherein administration of the sterol composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions, when administered to a human.

83. The method of claim 82, wherein the difference in absorption of the sterol composition of the invention, when administered in the fed versus the fasted state, is

selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

84. The method of any one of claims 66-83, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

85. The composition of claim 84, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human.

86. The method of claim 84, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC, and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max}, when administered to a human.

87. The method of any one of claims 66-86, wherein the T_{max} of the sterol, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a conventional, non-nanoparticulate form of the same sterol, administered at the same dosage.

88. The method of claim 87, wherein the T_{max} is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, and not greater than about 10% of the T_{max}, exhibited by a non-nanoparticulate formulation of the same sterol, administered at the same dosage.

89. The method of any one of claims 66-88, wherein the C_{max} of the sterol, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{max} for a conventional, non-nanoparticulate form of the same sterol, administered at the same dosage.

90. The method of claim 89, wherein the C_{max} is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the C_{max} exhibited by a non-nanoparticulate formulation of the same sterol, administered at the same dosage.

91. The method of any one of claims 66-90, wherein the AUC of the sterol, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of the same sterol, administered at the same dosage.

92. The method of claim 91, wherein the AUC is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the AUC exhibited by a non-nanoparticulate formulation of the same sterol, administered at the same dosage.

93. The method of any one of claims 66-92, additionally comprising administering one or more non-sterol active agents selected from the group consisting of:

(a) an active agent useful in treating dyslipidemia;

(b) an active agent useful in treating hyperlipidemia;

(c) an active agent useful in treating hypercholesterolemia;

(d) an active agent useful in treating cardiovascular disorders;

(e) an active agent useful in treating hypertriglyceridemia;

(f) an active agent useful in treating coronary heart disease;

(g) an active agent useful in treating peripheral vascular disease;

(h) an active agent useful as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and/or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb);

(i) an active agent useful as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia);

(j) an active agent useful in treating pancreatitis;

(k) an active agent useful in treating restenosis; and

(l) an active agent useful in treating Alzheimer's disease.

94. The method of any one of claims 66-93, additionally comprising administering one or more non-sterol active agents selected from the group consisting of cholesterol lowering agents, polycosanols, alkanoyl L-carnitines, antihypertensives, and statins.

95. The method of claim 94, wherein the cholesterol lowering agent is selected from the group consisting of ACE inhibitors, nicotinic acid, niacin, bile acid sequestrants, fibrates, vitamins, fatty acid derivatives, long chain plant extract alcohols, ezetimibe, and celluloses.

96. The method of claim 94, wherein the polycosanol is selected from the group consisting of (1) triacontanol, (2) hexacontanol, (3) ecocosanol, (4) hexacosanol, (5) tetracosanol, (6) dotriacontanol, (7) tetracontanol, (8) natural products comprising triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, or tetracontanol; and (9) extracts of natural products comprising triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, or tetracontanol.

97. The method of claim 94, wherein the antihypertensive is selected from the group consisting of diuretics, beta blockers, alpha blockers, alpha-beta blockers, sympathetic nerve inhibitors, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin receptor blockers.

98. The method of claim 94, wherein the statin is selected from the group consisting of atorvastatin; a 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivative other than atorvastatin; lovastatin; a keto analog of mevinolin other than lovastatin; pravastatin; simvastatin; velostatin; fluindostatin; pyrazole analogs of mevalonolactone derivatives; rivastatin; a pyridyldihydroxyheptenoic acid other than rivastatin; SC-45355; dichloroacetate; imidazole analogs of mevalonolactone; 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives; 2,3-di-substituted pyrrole derivatives; 2,3-di-substituted furan derivatives; 2,3-di-substituted thiophene derivatives; naphthyl analogs of mevalonolactone; octahydronaphthalenes; and phosphinic acid compounds.

99. The method of any one of claims 66-98, wherein the subject is a human.

100. The method of any one of claims 66-99, wherein the method is used to treat a condition selected from the group consisting of hypercholesterolemia, hypertriglyceridemia, coronary heart disease, cardiovascular disorders, and peripheral vascular disease .

101. The method of any one of claims 66-99, wherein the method is used as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia.

102. The method of any one of claims 66-99, wherein the method is used as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia.

103. The method of any one of claims 66-99, wherein the method is used to decrease the risk of pancreatitis.

104. The method of any one of claims 66-99, wherein the method is used to decrease the risk of or to treat Alzheimer's disease.

105. The method of any one of claims 66-99, wherein the method is used to treat indications where lipid regulating agents are typically used.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/15410

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 A61K31/575

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SJOSTROM B ET AL: "A METHOD FOR THE PREPARATION OF SUBMICRON PARTICLES OF SPARINGLY WATER-SOLUBLE DRUGS BY PRECIPITATION IN OIL-IN-WATER EMULSIONS. II: INFLUENCE OF THE EMULSIFIER, THE SOLVENT, AND THE DRUG SUBSTANCE" JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, US, vol. 82, no. 6, 1 June 1993 (1993-06-01), pages 584-589, XP000367863 ISSN: 0022-3549 abstract page 585, right-hand column, paragraph 2 page 585, right-hand column, last paragraph -page 586, left-hand column, paragraph 4; figure 1 page 587, left-hand column, paragraph 3 - last paragraph; figure 5; table 2 -/--	1-105

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 2003	06/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/15410

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MULLER R H ET AL: "SOLID LIPID NANOPARTICLES (SLN) - AN ALTERNATIVE COLLOIDAL CARRIER SYSTEM FOR CONTROLLED DRUG DELIVERY" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 41, no. 1, 1995, pages 62-69, XP000482894 ISSN: 0939-6411 abstract paragraph '03.3!; figure 3	1-105
X	NAKAMURA K ET AL: "Enhancement of FITC-dextran absorption via nasal mucosa by nanoparticles based on 'beta!-sitosterol 'beta!-D-glucoside and its aglycon" S.T.P. PHARMA SCIENCES 2002 FRANCE, vol. 12, no. 1, 2002, pages 63-68, XP008022385 ISSN: 1157-1489 abstract paragraph '01.2!	1-105
X	WO 02 28204 A (KIM BO CHUN ;KIM KAB SIG (KR); HAN JUNG HEE (KR); HONG HYUNG PYO () 11 April 2002 (2002-04-11) page 4, line 27 -page 5, line 3 examples claims	1-105
X	WO 00 21490 A (HOLLENBROCK MARTINA ;FABRY BERND (DE); HENKEL KGAA (DE); FOERSTER) 20 April 2000 (2000-04-20) page 2, paragraph 2 - paragraph 3 examples 1-6 claims	1-105
X	WO 00 15329 A (HENKEL KGAA) 23 March 2000 (2000-03-23) page 2, paragraph 2 - paragraph 3 examples 1-5 claims	1-105
X	WO 01 00046 A (COGNIS DEUTSCHLAND GMBH ;SCHROEDER CHRISTINE (DE); DOLHAINE HANS () 4 January 2001 (2001-01-04) page 2, paragraph 2 - paragraph 3 examples claims	1-105

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/15410

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 66-105 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internation cation No
PCT/US 03/15410

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